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Clinical Lipidology Roundtable Discussion

JCL Roundtable: Diagnosis of severe familial hypercholesterolemia

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Abstract: The diagnosis of familial hypercholesterolemia is usually straightforward. The severely elevated low-density lipoprotein cholesterol and the occurrence of high concentrations of low-density lipoprotein cholesterol in the parents provide the diagnosis. The presence of tendon xanthomata is confirmation but not necessary. However, this relatively simple picture becomes much more complicated when one attempts to define the genetic variants that actually produced this clinical syndrome. In this Roundtable discussion, I am joined by two experts in the identification of genetic abnormalities discovered in those with phenotypic familial hypercholesterolemia. Dr. John Kane from the University of California, San Francisco, and Dr. Daniel Rader from the University of Pennsylvania share their knowledge in and experience with this topic.

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Dr. Brown: Let me start with a most difficult patient problem, a child younger than 5 years of age is referred because his pediatrician has discovered a low-density lipoprotein cholesterol (LDL-C) of 900 mg/dL. What should I do to refine the diagnosis?

Dr. Kane: First, I would like to decide whether this is a primary disorder of cholesterol metabolism. The most likely possibility is the genetically determined absence or dysfunction of LDL receptors, but other possibilities exist. One of the entities to think about would be homozygous phytosterolemia. This can be evaluated quickly by gas chromatographic analysis of sterols. This is a disease in which the body cannot eliminate plant sterols (phytosterols) such as sitosterol and


Dr. Brown


Dr. Rader

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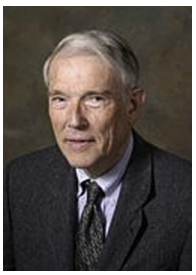
campesterol. These sterols may be identified as cholesterol in some analyses. In addition, phytosterol esters accumulate in circulating lipoproteins, especially LDL, along with cholesteryl esters, often leading to high serum cholesterol levels. These patients can have xanthomata that resemble those of homozygous familial hypercholesterolemia (FH). At least one other secondary dyslipidemia should be considered: cholestasis. We have seen patients with intrahepatic cholestasis with cholesterol levels >1000 mg/dL. They often have planar xanthomata of the skin.


Dr. Kane

D. Rader: Although this case has all the characteristics of so-called classic homozygous FH, I think Dr. Kane is absolutely right that one needs to always think about potential alternative diagnoses, particularly because both of those he mentioned have clear implications for therapy.

Dr. Brown: Family screening would be important in considering these conditions because one would not expect both parents to have elevated LDL-C. Having ruled out liver disease and found one or both parents to have elevated LDL-C, would not one expect to find at least 1 and quite likely 2 defective LDL receptor alleles?

Dr. Kane: Homozygosity for specific defective alleles at the LDL receptor locus is highly likely; however, a compound genetic state could be present with different defects at the LDL receptor on the 2 *LDL* receptor genes or a mixed heterozygous state with defects at other critical loci such as apolipoprotein B (*apoB*) or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) accompanying a single defective LDL receptor gene.

Dr. Brown: Do you have any statistics on the probability of true homozygosity vs mixed or compound heterozygosity? Is this a population-specific issue?

Dr. Rader: First, I think we need to clarify whether we are talking about true homozygosity, meaning the exact mutation in both alleles of the same gene (such as the *LDL* receptor), or compound heterozygosity, which is basically 2 different mutations but both in the same gene (such as the *LDL* receptor). The situation of double heterozygosity is also possible in which a mutation is found in 1 allele of 1 gene (such as the *LDL* receptor) and then another mutation in 1 allele of a different gene (such as *apoB*). All of these situations have the potential to produce a phenotype that resembles "homozygous FH." The most likely scenario is 2 different mutations in the *LDL* receptor. However, in regions where there is a founder effect with a specific LDL receptor mutation, or if there is consanguinity in the parents, the probability of having the same mutation in both alleles is considerably higher.

Two mutations are not always found even in patients who appear to have phenotypic homozygous FH. Some mutations are missed because of the nature of the sequencing. Dr. Kane, I do not know if you agree with this, but I would say that in a patient who presents with phenotypic homozygous FH, up to 20% of the patients cannot be identified to have mutations in both alleles.

Dr. Kane: That is true. So if all relevant defects are in the LDL receptor, we are really talking about 2 things here. The patient may have 2 defective but quite different alleles for the *LDL* receptor, one of which may be totally nonfunctional and the other a quantitatively defective receptor. In a mixed population such as the United States, this is the most frequent situation. However, the odds vary greatly when one looks at the heritage of each patient. If the patient is French Canadian or Lebanese or a South African "Afrikaner," the chances are much greater of having true homozygosity for an ablative mutation.

Dr. Brown: How reliable is history of consanguinity and how often do we find that?

Dr. Rader: With a history of consanguinity in the parents, one should suspect the possibility of the same mutations in both alleles. However, consanguinity is not always reliably reported in the medical and family history.

Dr. Brown: Practitioners should be aware that there are clusters of people, often in isolated environments, who have expanded in that setting from marriages between cousins and so forth. In this setting, a specific gene tends to be much more common, and the likelihood of it arriving twice in the same person is much higher. The French Canadians and Afrikaners in South Africa are classic examples. Then, of course, cultural issues can produce isolated populations such as the Lebanese Christians with resulting consanguinity. These are the settings in which true homozygous patients are found with some prevalence.

However, there are reports in well-defined patients in whom severe hypercholesterolemia occurs with normal sequences in 1 or both LDL receptor genes. This seems to be unexplained in some patients. Have we made any progress in that area? What are the candidates for other alleles, other genes that might be participating?

Dr. Kane: The *PCSK9* gene product has a key role in the elimination of the LDL receptor protein. Gain-of-function mutations at this locus can result in elevated LDL levels. As yet unidentified loci are likely causes, because in some cases genotyping has failed to reveal *LDL* receptor mutations. Some of these may prove to be epigenetic.

Dr. Brown: If a large number of people are screened for these genes related to elevated LDL-C, several gene variants are likely to be found, but often the variants do not provide an obvious molecular explanation for a disorder of LDL metabolism. Is that correct?

Dr. Kane: That is right. Combined effects can happen at different loci. In our lipid clinic in San Francisco we have documented several people who have an *LDL* receptor allele plus dysbetalipoproteinemia. We have another family with a defective *LDL* receptor allele plus familial combined hyperlipidemia that resulted in extremely aggressive coronary disease.

Dr. Brown: We should talk to the parents about a history of elevated LDL-C in the families. Would you not agree that examining the lipoproteins and the genes in both parents of